Peer Review Workshop on EPA's Draft External Review Document "Perchlorate Environmental Contamination: Toxicological Review and Risk Characterization"

March 5–6, 2002

CHARGE TO THE REVIEWERS

Introduction and Background

Perchlorate (ClO_4^-) is an anion that originates as a contaminant in groundwater and surface waters from the dissolution of its ammonium, potassium, magnesium, or sodium salts. Perchlorate is exceedingly mobile in aqueous systems and can persist for many decades under typical groundwater and surface water conditions. A major source of perchlorate contamination is the manufacture of ammonium perchlorate for use as the oxidizer component and primary ingredient in solid propellant for rockets, missiles, and fireworks.

EPA issued a provisional toxicity assessment for perchlorate in 1992 and a revised provisional assessment in 1995 based on the effects of potassium perchlorate in patients with Graves' disease, an autoimmune disease that results in hyperthyroidism. In March 1997, the existing toxicologic database on perchlorate was determined to be inadequate for quantitative human health risk assessment by an independent non-EPA external peer review panel. A lack of data on the ecotoxicological effects was also noted. In May 1997, a perchlorate testing strategy was developed based on the known mode-of-action for perchlorate toxicity (the inhibition of iodide uptake in the thyroid and subsequent perturbations of thyroid hormone homeostasis), and an accelerated research program was initiated to gain a better understanding of the human health effects of perchlorate, examine possible ecological impacts, refine analytical methods, develop treatment technologies, and better characterize the occurrence of perchlorate in groundwater and surface waters.

In December 1998, the National Center for Environmental Assessment (NCEA) developed an external peer review draft document that assessed the human health and ecological risk of perchlorate ("Perchlorate Environmental Contamination: Toxicology Review and Risk Characterization Based on Emerging Information," NCEA-1-0503). This document presented a human health risk assessment that incorporated results of the newly performed health effects studies available as of November 1998 from the perchlorate testing strategy and a screening-level ecological assessment. The human health risk assessment utilized a model motivated by the mode-of-action that harmonized noncancer and cancer approaches to derive a single oral risk benchmark based on precursor effects for both altered neurodevelopment and thyroid neoplasia. A workshop was convened by the Agency in February 1999 in San Bernardino, California, to provide external peer review of that document. The external scientific peer review panel endorsed the conceptual approach proposed by NCEA, but recommended that new analyses be conducted and that several additional studies be planned and performed. NCEA has prepared a revised perchlorate assessment that addresses comments from the 1999 external peer review workshop and incorporates data from additional studies that have become available since the 1999 review. These supporting data and the revised draft assessment are the subject of the current external peer review.

Specific objectives of this draft assessment are to derive a human health risk estimate for perchlorate based both on its potential to cause noncancer toxicity or cancer, to provide a screening ecological risk assessment for perchlorate, and to evaluate the evidence for indirect exposures, i.e., those exposures not occurring by direct ingestion of contaminated water.

Disclaimer

This draft external review document is still undergoing scientific review and deliberations both by the external scientific community and within the Agency. As with any EPA draft assessment document containing a quantitative risk value, that risk value is also draft and should not at this stage be construed to represent EPA policy.

Purpose of the Peer Review

The Agency conducts external peer reviews of draft assessments to ensure that science is used credibly and appropriately in the derivation of human health and ecotoxicological assessments. After the scientific basis of these draft assessments has been peer reviewed, the documents are forwarded to the IRIS Consensus Process for final approval and adoption by the EPA. These hazard and dose-response assessments will then appear on IRIS and become available as Agency consensus risk information. You have been chosen to participate in the external peer review of the "Toxicological Review and Risk Characterization for Perchlorate" as an expert in a scientific discipline relevant to the perchlorate assessment, including reproductive and developmental toxicology, neurotoxicology, immunotoxicology, genetic toxicology, pathology, epidemiology, endocrinology, statistics, physiologically-based pharmacokinetic (PBPK) modeling, ecotoxicology, environmental fate and transport, or risk assessment. The charge to the external peer reviewers has two main components:

(1) To review the protocols, performance and results of studies that have been performed since the 1999 peer review that are not in the peer-reviewed literature (Note that these studies include PBPK models).

(2) To review the draft risk assessment and evaluate whether the data chosen and inferences based on the data employed in the derivation of the assessments are appropriate and scientifically sound.

Please note that you are *not* asked to review the recommended Agency testing or risk assessment guidelines or methodologies used to derive the human health or ecotoxicological assessments, because these have undergone independent review by external scientific peers, the public, and EPA Science Advisory Boards. However, we do ask that you comment on the application of these guidelines and methodologies within the assessment as you deem appropriate. For reference, the preface to the draft document lists the various Agency guidelines and methodologies that were considered when developing the perchlorate assessment.

Instructions to Reviewers

The peer review meeting will be structured around the charge questions that follow, which are organized into eight topic areas. The charge questions seek the panel's critical input on two topics:

- Studies published since 1999 that have not undergone peer review.
- EPA's interpretation of these and other studies in the perchlorate assessment.

Reviewers are not being asked to respond to every charge question, but instead have been assigned responsibilities based on their areas of expertise. Table 1 lists the reviewers' responsibilities. As the table indicates, reviewers are being asked to perform the following tasks:

- **Studies:** Almost every reviewer is being asked to review some of the studies published since 1999 that require peer review. Table 1 identifies the studies to which each reviewer has been assigned, and Table 2 gives the full citations for these studies. Copies of the studies were distributed to the reviewers, according to the assignments in Table 1. Attachments 1 and 3 present questions to guide your reviews of these studies. The questions in Attachment 1 pertain to human health, laboratory animal, and ecological studies. The questions in Attachment 3 pertain to PBPK studies. Please *consider* the questions in these attachments as you review the studies. *You do not need to answer every question in the attachments, rather use your professional judgment to address those that are most appropriate to the study in question.*

- **Perchlorate assessment:** Every reviewer is being asked to read the entire perchlorate assessment and review specific sections of the document. Table 1 identifies the specific sections that each reviewer has been assigned to review. It also lists the charge questions that you must answer, both in your premeeting comments and at the meeting. Attachment 2 provides a list of questions which give you the context for answering the charge questions B2, C2, D2, and E2. Please *consider* the questions in Attachment 2 as you review the document. *You do not need to answer every question in the attachment, rather use your professional judgment to address those that are most appropriate to the chapter in question.*

Though not required, you are encouraged to respond to charge questions other than those to which you have been assigned as time allows. At the peer review meeting, the reviewers will discuss their responses to the charge questions, with the goal of providing EPA with recommendations on how to improve the document. Table 1 identifies the peer reviewers who will serve as discussions leaders and moderate these discussions.

SPECIFIC CHARGE QUESTIONS ORGANIZED BY TOPIC AREA

Topic Area A: **Hazard Characterization and Mode of Action**
Designated reviewers: **All reviewers (except William Adams and Teresa Fan)**
Discussion leader: **Thomas Zoeller**

A.1 Have all relevant data on toxicokinetics and toxicodynamics been identified and appropriately utilized? Have the similarities and differences in the toxicity profile across species been adequately characterized?

A.2 The EPA has framed a conceptual model based on the key event for the mode of action of perchlorate as inhibition of iodide uptake at the sodium (Na^+)-iodide (I^-) symporter (NIS). Are the roles and relative importance of the key event and subsequent neurodevelopmental and neoplastic sequelae clearly articulated and consistent with the available data on anti-thyroid agents or conditions and with the physicochemical and biological properties of perchlorate?

A.3 The 1999 peer review panel agreed with EPA that perchlorate was not likely to directly interact with DNA. What inferences can be made, based on consideration of the mode-of-action data, to inform the choice of dose metric and the approach for low-dose extrapolation?

A.4 A harmonized approach to characterize the potential risk of both noncancer and cancer toxicity has been proposed based on the key event of iodide uptake inhibition. Comment on whether the approach is protective for both.

Topic Area B: **Human Health Effects Data**
Designated reviewers: **Nancy Carrasco, Tony Cox, David Hoel, Mehdi Razzaghi, Ron Wyzga, Thomas Zoeller**
Discussion leader: **David Hoel, with Nancy Carrasco for clinical endocrinology and Mehdi Razzaghi for observational epidemiology**

B.1 Do any of the studies published since 1999 that have not undergone peer review have any notable limitations and deficiencies? Refer to Table 2 for a listing of the specific studies relevant to this topic area. Please consider the questions in Attachment 1 when formulating your response. You do not need to answer every question in Attachment 1, rather use your professional judgment to address those that are most appropriate to the study in question.

B.2 Please consider the questions in Attachment 2 when preparing written comments on how EPA analyzed, interpreted, and presented results of these studies in the perchlorate assessment. You do not need to answer every question in Attachment 2, rather use your professional judgment to address those that are most appropriate to the chapter in question.

B.3 Have the epidemiological studies been adequately summarized as a basis for the hazard characterization?

B.4 Are the exposure measures constructed from data in the epidemiological studies sufficient to permit meaningful bounding of the predicted dose-response estimates derived from extrapolation of the laboratory animal studies?

B.5 Are the associations observed in the epidemiological data consistent with the proposed mode of action? Did the experimental design have sufficient power to accurately ascertain the association between perchlorate exposure and the specific outcome(s)? Were confounding factors appropriately controlled?

Topic Area C: **Laboratory Animal Studies**
Designated reviewers: **Michael Aschner, Michael Collins, Thomas Collins, Tony Cox, David Jacobson-Kram, Loren Koller, Merle Paule, Gary Williams,Ron Wyzga, Thomas Zoeller**
Discussion leader: **Multiple reviewers (see Table 1)**

C.1 Do any of the studies published since 1999 that have not undergone peer review have any notable limitations and deficiencies? Refer to Table 2 for a listing of the specific studies relevant to this topic area. Please consider the questions in Attachment 1 when formulating your response. You do not need to answer every question in Attachment 1, rather use your professional judgment to address those that are most appropriate to the study in question.

C.2 Please consider the questions in Attachment 2 when preparing written comments on how EPA analyzed, interpreted, and presented results of these studies in the perchlorate assessment. You do not need to answer every question in Attachment 2, rather use your professional judgment to address those that are most appropriate to the chapter in question.

C.3 Are the toxicity data consistent with the proposed mode of action for perchlorate?

C.4 The Toxicological Review and Risk Characterization Document assigned no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) in most of the studies discussed in the document. Are the NOAELs/LOAELs appropriate? Please explain.

Topic Area D: **Ecological Risk Assessment and Evidence for Indirect Exposure**
Designated reviewers: **William Adams, Teresa Fan**
Discussion leader: **William Adams**

D.1 Do any of the studies published since 1999 that have not undergone peer review have any notable limitations and deficiencies? Refer to Table 2 for a listing of the specific studies relevant to this topic area. Please consider the questions in Attachment 1 when formulating your response. You do not need to answer every question in Attachment 1, rather use your professional judgment to address those that are most appropriate to the study in question.

D.2 Please consider the questions in Attachment 2 when preparing written comments on how EPA analyzed, interpreted, and presented results of these studies in the perchlorate assessment. You do not need to answer every question in Attachment 2, rather use your professional judgment to address those that are most appropriate to the chapter in question.

D.3 Comment on whether the assays selected for evaluation in the ecological screening and site-specific analyses can be reasonably expected to identify potential ecological effects of concern.

D.4 Comment on whether the goals and objectives of this ecological screening analysis have been adequately described and to what extent these have been met.

D.5 Do the analyses support the summary and conclusions presented? Are relevant and important aspects of uncertainty addressed sufficiently?

D.6 Comment on the strengths and limitations of the available data to characterize transport and transformation of perchlorate in the environment, including soil, plants and animals.

D.7 Comment on the strengths and limitations of the available data to suggest sources of perchlorate exposure other than drinking water.

Topic Area E: **Use of PBPK Modeling**
Designated reviewers: **Michael Kohn, Kannan Krishnan**
Discussion leader: **Michael Kohn**

E.1 For each of the four models developed by the Air Force Research Laboratory (AFRL) listed below, consider the questions in Attachment 3 and comment as necessary. You do not need to answer every question in Attachment 3, rather use your professional judgment to address those that are most appropriate to the model and associated consultative letters/studies in question. Refer to Table 1 for all relevant citations. Note that the citations for the four models, which are contained in consultative letters, follow:

Adult Male Rat Model (Merrill, 2001c)
Adult Human Model (Merrill, 2001d)
Pregnant Rat and Fetus Model (Clewell, 2001a)
Lactating Rat and Neonate Model (Clewell, 2001b)

E.2 Please consider the questions in Attachment 2 to comment on how EPA applied and presented the models in the perchlorate assessment. You do not need to answer every question in Attachment 2, rather use your professional judgment to address those that are most appropriate to the chapter in question.

Topic Area F: **Human Health Dose-Response Assessment**
Designated reviewers: **All reviewers (except William Adams and Teresa Fan)**
Discussion leader: **Thomas Collins**

F.1 Are the conclusions and conditions regarding the key event and the weight of the evidence for effects after oral exposure to perchlorate appropriate and consistent with the information on mode of action? Have the diverse data been integrated appropriately and do they support the proposed point of departure? Should any other data be considered in arriving at a point of departure?

F.2 Comment on the use of the PBPK models for interspecies extrapolation and the choice of the dose metric.

F.3 Are there other data which should be considered in developing the uncertainty factors? Do you consider that the data support the values proposed or different values for each? Do the confidence statements accurately reflect the relevancy of the critical effects to humans and the comprehensiveness of the database? Do these statements make all the underlying assumptions and limitations of the assessment apparent? If not, what needs to be added?

F.4 Have all the factors influencing susceptibility been clearly described and accounted for in the assessment?

Topic Area G: **Risk Characterization**
Designated reviewers: **Question G.1: All reviewers (except William Adams and Teresa Fan)**
Question G.2: William Adams and Teresa Fan
Discussion leader: **Ron Wyzga**

G.1 Does the risk characterization chapter adequately and clearly summarize the salient aspects of the human health risk posed by potential perchlorate exposures?

G.2 Does the risk characterization chapter adequately and clearly summarize the salient aspects of the ecotoxicological risk posed by potential perchlorate exposures?

Topic Area H: **General Comments, Conclusions, and Recommendations**
Designated reviewers: **All reviewers**
Discussion leader: **Ron Wyzga**

H.1 Please provide comments on additional topics relevant to the perchlorate assessment, but not explicitly addressed in the previous charge questions.

H.2 Please identify specific sections of the document you find unclear or difficult to understand and explain why.

Table 1
Reviewer Assignments

Reviewer Name	Studies Published Since 1999 to Review	Chapters of the EPA Document to Review	Charge Questions to Answer	Discussion Leader Responsibilities
William Adams	Condike 2001 EA Engineering 1999 EA Engineering 2000 Parsons Engr. Sci. 2001	Chapters 1-3, 8, 9, 10	D1-D7, G2, H1-H2	Topic Area D
Michael Aschner	Argus 2001 Bekkedal et al. 2000	Chapters 1-3, 5, 7, 10	A1-A4, C1-C4, F1-F4, G1, H1-H2	Topic Area C (Neurotoxicity only)
Nancy Carrasco	Greer 2000 Lawrence 2001 Merrill 2001a	Chapters 1-3, 4, 7, 10	A1-A4, B1-B5, F1-F4, G1, H1-H2	Topic Area B (Clinical Endocrinology)
Michael Collins	Argus 2000	Chapters 1-3, 5, 7, 10	A1-A4, C1-C4, F1-F4, G1, H1-H2	Topic Area C (Developmental only)
Thomas Collins	Argus 1999	Chapters 1-3, 5, 7, 10	A1-A4, C1-C4, F1-F4, G1, H1-H2	Topic Area C (Reproductive only) Topic Area F
Tony Cox	Greer 2000 Lawrence 2001 Merrill 2001a	Chapters 1-3, 4, 5, 7, 10	A1-A4, B1-B5, C1-C4, D1-D7, F1-F4, G1, H1-H2	Topic Area C (Statistical Issues)
Teresa Fan	Condike 2001 EA Engineering 1999 EA Engineering 2000 Parsons Engr. Sci. 2001	Chapters 1-3, 8, 9, 10	D1-D7, G2, H1-H2	None
David Hoel	Greer 2000 Lawrence 2001 Merrill 2001a	Chapters 1-3, 4, 7, 10	A1-A4, B1-B5, F1-F4, G1, H1-H2	Topic Area B (Statistical Issues)
David Jacobson-Kram	None	Chapters 1-3, 5, 7, 10	A1-A4, C1-C4, F1-F4, G1, H1-H2	Topic Area C (Genetic Toxicity Issues)

Table 1 (Continued)
Reviewer Assignments

Reviewer Name	Studies Published Since 1999 to Review	Chapters of the EPA Document to Review	Charge Questions to Answer	Discussion Leader Responsibilities
Michael Kohn	Merrill 2001a Merrill 2001c Merrill 2001d Merrill 2001e Clewell 2001a Clewell 2001b Yu 2000, 2001, 2002 Yu et al. 2000 Mahle 2000, 2001	Chapters 1–3, 6, 7, 10	A1–A4, E1–E2, F1–F4, G1, H1-H2	Topic Area E
Loren Koller	BRT Burl. Res. Tech. 2000a BRT Burl. Res. Tech. 2000b BRT Burl. Res. Tech. 2000a Keil et al. 1999	Chapters 1–3, 5, 7, 10	A1–A4, C1–C4, F1–F4, G1, H1-H2	Topic Area C (Immunotoxicity only)
Kannan Krishnan	Merrill 2001a Merrill 2001c Merrill 2001d Merrill 2001e Clewell 2001a Clewell 2001b Yu 2000, 2001, 2002 Yu et al. 2000 Mahle 2000, 2001	Chapters 1–3, 6, 7, 10	A1–A4, E1–E2, F1–F4, G1, H1-H2	None
Merle Paule	Argus 2001 Bekkedal et al. 2000	Chapters 1–3, 5, 7, 10	A1–A4, C1–C4, F1–F4, G1, H1-H2	None
Mehdi Razzaghi	Greer 2000 Lawrence 2001 Merrill 2001a	Chapters 1–3, 4, 7, 10	A1–A4, B1–B5, F1–F4, G1, H1-H2	Topic Area B (Observational Epidemiology)

Table 1 (Continued)
Reviewer Assignments

Reviewer Name	Studies Published Since 1999 to Review	Chapters of the EPA Document to Review	Charge Questions to Answer	Discussion Leader Responsibilities
Gary Williams	Argus 2001	Chapters 1–3, 5, 7, 10	A1–A4, C1-C4, F1–F4, G1, H1-H2	Topic Area C (Pathology only)
Ron Wyzga	None	Chapters 1–3, 5, 7, 10	A1–A4, B1–B5, C1-C4, F1–F4, G1, H1-H2	Topic Areas G and H
Thomas Zoeller	Argus 2001 Bekkedal et al. 2000 Greer 2000 Lawrence 2001 Merrill 2001a	Chapters 1–3, 4, 5, 7, 10	A1–A4, B1–B5, C1–C4, F1–F4, G1, H1-H2	Topic Area A; Topic Area C (Endocrine and neuroendocrine only)

Table 2
Studies Conducted Since 1999 That Require Peer Review

Topic Area	Relevant Studies
Human health effects data: Topic Area B	Greer (2000). Does environmental perchlorate exposure alter human thyroid function? Determination of the dose-response for inhibition of radioiodine uptake. In: Abstracts of the 12th International Thyroid Congress; October; Kyoto, Japan. Endocrine J. 47 (suppl.): 146.
	Lawrence (2001). Low dose perchlorate (3 mg daily) and thyroid function [letter]. Thyroid 11: 295.
	Merrill, E. (2001a) Consultative letter, AFRL-HE-WP-CL-2001-0004, QA/QC audit report for the study of perchlorate pharmacokinetics and inhibition of radioactive iodine uptake (RAIU) by the thyroid in humans (CRC protocol #628) [memorandum with attachments to Annie Jarabek]. Wright-Patterson AFB, OH: Air Force Research Laboratory; May 10.
Laboratory animal studies: Topic Area C (Reproductive Toxicity)	Argus Research Laboratories, Inc. (1999) Oral (drinking water) two-generation (one litter per generation) reproduction study of ammonium perchlorate in rats. Horsham, PA: Argus Research Laboratories, Inc.; protocol no. 1416-001.
Laboratory animal studies: Topic Area C (Developmental Toxicity)	Argus Research Laboratories, Inc. (2000) Oral (drinking water) developmental toxicity study of ammonium perchlorate in rats. Horsham, PA: Argus Research Laboratories, Inc.; protocol no. 1416-003D.
Laboratory animal studies: Topic Area C (Neurodevelopmental Toxicity)	Argus Research Laboratories, Inc. (2001) Hormone, thyroid and neurohistological effects of oral (drinking water) exposure to ammonium perchlorate in pregnant and lactating rats and in fetuses and nursing pups exposed to ammonium perchlorate during gestation or via maternal milk. Horsham, PA: Protocol no. ARGUS 1416-003.
	Bekkedal, M. Y. V.; Carpenter, T.; Smith, J.; Ademujohn, C.; Maken, D.; Mattie, D. R. (2000) A neurodevelopmental study of the effects of oral ammonium perchlorate exposure on the motor activity of pre-weaning rat pups. Wright-Patterson Air Force Base, OH: Naval Health Research Center Detachment, Neurobehavioral Effects Laboratory; report no. TOXDET-00-03.
	Mahle, D. (2000). Consultative letter, AFRL-HE-WP-CL-2000-0043, hormone and perchlorate data from cross-fostering study [memorandum with attachments to Annie M. Jarabek]. Wright-Patterson Air Force Base, OH: Air Force Research Laboratory; October 11.
	Mahle, D. (2001). Consultative letter, AFRL-HE-WP-CL-2001-0001, hormone and perchlorate data from cross-fostering study [memorandum with attachments to Annie M. Jarabek]. Wright-Patterson Air Force Base, OH: Air Force Research Laboratory; May 1.

Table 2 (Continued)
Studies Conducted Since 1999 That Require Peer Review

Topic Area	Relevant Studies
Laboratory animal studies: Topic Area C (Immunotoxicity)	BRT-Burleson Research Technologies, Inc. (2000a) Ammonium perchlorate: effect on immune function. Quality assurance audit: study no. BRT 19990524 -- plaque-forming cell (PFC) assay; study no. BRT 19990525– local lymph node assay (LLNA) in mice. Raleigh, NC.
	BRT-Burleson Research Technologies, Inc. (2000b) Addendum to study report: ammonium perchlorate: effect on immune function [with cover letter dated August 31 from G. R. Burleson]. Raleigh NC.
	BRT-Burleson Research Technologies, Inc. (2000c) Ammonium perchlorate: effect on immune function. Raleigh, NC: BRT 19990524 study protocol: plaque-forming cell (PFC) assay; BRT 19990525 study protocol: local lymph node assay (LLNA) in mice.
	Keil, D.; Warren, D. A.; Jenny, M.; EuDaly, J.; Dillard, R. (1999) Effects of ammonium perchlorate on immunotoxicological, hematological, and thyroid parameters in B6C3F1 female mice. Final report. Charleston, SC: Medical University of South Carolina, Department of Medical Laboratory Sciences; report no. DSWA01-97-0008.
Ecological risk assessment: Topic Area D	Condike (2001). Perchlorate data in fish and plants [letter with attachments to Annie M. Jarabek]. Fort Worth, TX: Department of the Army, Fort Worth District, Corps of Engineers; December 21.
	EA Engineering (1999). Results of algal toxicity testing with sodium perchlorate. Sparks, MD: EA Engineering, Science, and Technology, Inc.
	EA Engineering (2000). Results of chronic toxicity testing with sodium perchlorate using *Hyalella azteca* and *Pimephales promelas*. Sparks, MD: report number 3505.
	Parsons Engineering Science, Inc. (2001) Scientific and technical report for perchlorate biotransport investigation: a study of perchlorate occurrence in selected ecosystems. Interim final. Austin, TX; contract no. F41624-95
Use of PBPK modeling: Topic Area E	Merrill, E. A.(2001a) Consultative letter, AFRL-HE-WP-CL-2001-0004, QA/QC audit report for the study of perchlorate pharmacokinetics and inhibition of radioactive iodine uptake (RAIU) by the thyroid in humans (CRC protocol #628) [memorandum with attachments to Annie Jarabek]. Wright-Patterson AFB, OH: Air Force Research Laboratory; May 10.
	Merrill, E. A. (2001c) Consultative letter, AFRL-HE-WP-CL-2001-0005, PBPK model for iodide kinetics and perchlorate-induced inhibition in the male rat [memorandum with attachments to Annie Jarabek]. Wright-Patterson AFB, OH: Air Force Research Laboratory; May 8.
	Merrill, E. A. (2001d) Consultative letter, AFRL-HE-WP-CL-2001-0008, PBPK model for perchlorate-induced inhibition of radioiodide uptake in humans [memorandum with attachments to Annie Jarabek]. Wright-Patterson AFB, OH: Air Force Research Laboratory; June 5.

Table 2 (Continued)
Studies Conducted Since 1999 That Require Peer Review

Topic Area	Relevant Studies
Use of PBPK modeling: Topic Area E (Continued)	Merrill, E. A. (2001e) Consultative letter, AFRL-HE-WP-CL-2001-0010, comparison of internal dosimetrics using PBPK models for perchlorate induced inhibition of thyroid iodide uptake and sensitivity analysis for male rat model [memorandum with attachments to Annie Jarabek]. Wright-Patterson AFB, OH: Air Force Research Laboratory; December 20.
	Clewell, R. A. (2001a) Consultative letter, AFRL-HE-WP-CL-2001-0006, physiologically-based pharmacokinetic model for the kinetics of perchlorate-induced inhibition of iodide in the pregnant rat and fetus [memorandum with attachments to Annie Jarabek]. Wright-Patterson AFB, OH: Air Force Research Laboratory; May 10.
	Clewell, R. A. (2001b) Consultative letter, AFRL-HE-WP-CL-2001-0007, physiologically-based pharmacokinetic model for the kinetics of perchlorate-induced inhibition of iodide in the lactating and neonatal rat [memorandum with attachments to Annie Jarabek]. Wright-Patterson AFB, OH: Air Force Research Laboratory; May 24.
	Yu, K. O. (2000) Consultative letter, AFRL-HE-WP-CL-2000-0038, tissue distribution and inhibition of iodide uptake in the thyroid by perchlorate with corresponding hormonal changes in pregnant and lactating rats (drinking water study) [memorandum with attachment to Annie Jarabek]. Wright-Patterson Air Force Base, OH: Air Force Research Laboratory; June 28.
	Yu, K. O.; Todd, P. N.; Young, S. M.; Mattie, D. R.; Fisher, J. W.; Narayanan, L.; Godfrey, R. J.; Sterner, T. R.; Goodyear, C. (2000) Effects of perchlorate on thyroidal uptake of iodide with corresponding hormonal changes. Wright-Patterson AFB, OH: Air Force Research Laboratory; report no. AFRL-HE-WP-TR
	Yu, K.O. (2001). Consultative letter, AFRL-HE-WP-CL-2002-0001, intravenous kinetics of radiolabeled iodide in tissues of adult male Sprague Dawley rat dosed with $^{125}I^-$ plus carrier [memorandum with attachments to Annie M. Jarabek]. Wright-Patterson Air Force Base, OH: Air Force Research Laboratory; December 21.
	Yu, K.O. (2002). Consultative letter, AFRL-HE-WP-CL-2002-0002, intravenous kinetics of radiolabled iodide and perchlorate in tissues of pregnant and lactating Sprague Dawley female rats dosed with perchlorate and/or carrier free $^{125}I^-$ [memorandum with attachment to Annie M. Jarabek]. Wright-Patterson Air Force Base, OH: Air Force Research Laboratory; January 7.
	Mahle, D. (2000). Consultative letter, AFRL-HE-WP-CL-2000-0043, hormone and perchlorate data from cross-fostering study [memorandum with attachments to Annie M. Jarabek]. Wright-Patterson Air Force Base, OH: Air Force Research Laboratory; October 11.
	Mahle, D. (2001). Consultative letter, AFRL-HE-WP-CL-2001-0001, hormone and perchlorate data from cross-fostering study [memorandum with attachments to Annie M. Jarabek]. Wright-Patterson Air Force Base, OH: Air Force Research Laboratory; May 1.

Attachment 1

General Considerations for Evaluating the Human Health, Laboratory Animals, and Ecological Studies listed in Table 2 (Note: Refer to Attachment 3 for general considerations for evaluating the PBPK models.)

Note to Reviewers: *These questions are being provided as general considerations for reviewing the studies published since 1999 that require peer review. You do not need to answer every question below when reviewing the studies that have been assigned to you; rather use your professional judgment to address those that are most appropriate to the study in question.*

1. Please review the strengths and limitations of the experimental protocol of the study. Are the objectives being investigated in each study clearly identified? Is the study design appropriate to address these objectives? Does the study design represent the state-of-the science? Discuss all limitations in experimental design that would affect the ability to interpret significance of the study results. Also indicate where insufficient information has been provided on the experimental design.

2. Please note any limitations in performance of the study that could decrease the relevance of the study findings. For example, were the studies conducted in accordance with Good Laboratory Practices or specific testing guidance? Did the study include QA/QC? Were there occurrences that necessitated a change to the protocol during the course of the study? If so, what impact did these changes have on the findings?

3. Were dosing or exposure measures appropriately formulated or controlled? Were appropriate endpoints and time points utilized? Were sufficient numbers employed to observe an effect?

4. Please comment on the strengths and limitations of the statistical analyses used to evaluate the study findings. What other statistical analyses, if any, should be performed?

5. Please comment on the strengths and limitations of the inferences made and presentation of the results in the study report. Were sufficient data presented in the report and its appendices to confirm the findings presented therein? Are the conclusions of the report supported by the data? Please explain.

6. Overall, was the study as designed, performed and reported of sufficient quality for use in hazard identification purposes? Is it important to enhancing the toxicological / ecotoxicological risk characterization of perchlorate exposures? If so, indicate the extent to which it can be used for characterizing adverse effects.

7. Do the finding provide information relevant to the evaluating the sensitivities of specific subpopulations (e.g., infants, children, hypothyroxinemic or hypothyroid individuals, pregnant women) of exposed individuals and potential effects?

Attachment 2

General Questions for Reviewing the Topic Areas

Note to Reviewers: *These questions are being provided as general considerations for reviewing how EPA interpreted and analyzed data from the various perchlorate studies. You do not need to answer every question below when answering charge questions B:2, C.2, D.2, and E.2; rather use your professional judgment to address the questions that you see being most relevant.*

1. Are you aware of any other data or studies that are relevant (i.e., useful for the hazard identification or dose-response assessment) for the assessment of adverse health (both noncancer and cancer) or ecological effects of perchlorate? Note any references that have not been cited and their relevance to the hazard characterization.

2. Have the key aspects of the protocols, conduct and results of each study been adequately described in the Toxicological Review and Risk Characterization Document? Where limitations exist in study reports or published papers, have they been adequately discussed? Please make specific recommendations on improvements to the discussion of the studies.

- Indicate the strengths and limitations of the analyses performed on the data in Toxicological Review and Risk Characterization Document, first of the specific toxicological studies and then of the overall toxicology database on perchlorate. Has the document adequately evaluated and integrated the results of all relevant studies to capture the biological relevance of the entire database? Where inconsistencies appear to exist in the findings among studies with respect to perturbation of the hypothalamic-pituitary-thyroid axis, does the document adequately address such inconsistencies? Enumerate specific improvements that should be made, if any.

- Authors of the Toxicological Review and Risk Characterization Document in some cases have performed statistical analyses beyond those in the original study reports. Where these statistical analyses were performed, were they appropriate? Did they add to the overall understanding and relevance of the studies? Were the appropriate endpoints, receptors/indicators or time points used? Please make specific recommendations regarding data, methods and inferences.

- Are the key issues, statements, and conclusions clearly stated? Are the conclusions supported with sufficient data and arguments? How would you suggest improving the clarity of the text. Please make specific recommendations or note revisions that would improve the usefulness of the document for the purposes of characterizing the human health and ecotoxicological effects of perchlorate.

- Are the assumptions and uncertainties clearly and adequately expressed?

Attachment 3

General Considerations for Evaluating the Proposed PBPK Models Listed in Table 2

Note to Reviewers: *These questions are being provided as general considerations for reviewing the PBPK models contained in the consultative letters, and other documents published since 1999 that require peer review. You do not need to answer every question below when reviewing these models and associated materials and responding to charge question E.1; rather use your professional judgment to address those that are most appropriate to the model or consultative letter in question.*

1. ***Structure.*** Disposition is defined as absorption, distribution, metabolism and elimination (ADME).

   Does the proposed model structure contain the necessary anatomical compartments and physiological processes to accurately describe perchlorate disposition? Or iodide disposition?

   Uptake into the thyroid is described by an active (Michaelis-Menten) process and a permeability area for first-order movement of the anions between the subcompartments. Please comment on the advantages and limitations of this approach. Does it capture all the relevant behavior for the competitive inhibition of iodide uptake by perchlorate and distribution in the thyroid?

   Comment on the approach for describing perchlorate's plasma protein binding and dissociation.

2. ***Parameterization.*** Consider whether the experimental data or literature, fitting routines, and scaling assumptions were appropriate and adequate to support the values for the various species-specific and chemical-specific parameters used in each model structure. To describe perchlorate disposition? For iodide disposition? Are the parameters derived by fitting to available data reasonable and reliable?

   Comment on the "upregulation" adjustment of the Vmaxc_T*p* to represent upregulation of the NIS with increasing dose of perchlorate.

   Comment on the approach to growth of maternal and fetal parameters.

3. ***Validation.*** The models were validated to varying degrees with available data that were not used to estimate the parameters. Has sufficient validation of the structures been achieved?

4. ***Application.*** The models are being used to develop human equivalent exposures (HEE) for different dose metrics for dose-response modeling in Chapter 7.

   Comment on the utility of the proposed PBPK structures in the parallelogram approach.

   Comment on the advantages, limitations, and reliability of these models to describe an HEE for different dose metrics and the correlation between the two:

   - Area under the curve of perchlorate in the blood (AUCB)
   - Iodide uptake inhibition

5. ***Variability and Uncertainty.*** Comment on the variability in underlying data and resultant model structures. What are the uncertainties inherent in using these models for the applications to derive human equivalent exposures for interspecies extrapolation based on the different dose metrics? Are the uncertainties associated with the PBPK modeling similar to, or reduced, in relation to default approaches?